with conventional chemical enhancers. Physical enhancers have therefore been investigated to create wider pathways through the epidermis, using electric voltage, a process known as electroporation (1), or by using ultrasound, a process referred to as sonophoresis (or phonophoresis). On the other hand, the use of powerful techniques to overcome the skin barrier is limited by potential damage to the skin (1, 2).

The use of ultrasound as a transdermal transport enhancer, i.e., sonophoresis or phonophoresis, became very popular in sports medicine for local treatment of minor injuries and is believed both to accelerate functional recovery and to increase transdermal transport of topically applied drugs, especially nonsteroidal antiinflammatory drugs (3, 4). Using 1 to 3 MHz ultrasound, the extent of the drug transport enhancement still remains fairly low or is not even significant in some studies, as pointed out in a Cochrane systematic review published in 2014 (5). However, the feasibility of making the skin permeable to treatments such as insulin (6–8) or low-molecular-weight heparin (9) by using low-frequency ultrasound has increased the interest for the application of this noninvasive method in human medicine (1, 10–13).

43.2 PHYSICAL CHARACTERISTICS OF ULTRASOUND

Ultrasound is generated by a piezoelectric crystal transducer, which converts electric power into a mechanical oscillation generating an acoustic wave. After its emission, the wave is transmitted in an aqueous coupling medium (air or gas are bad transmitter media for ultrasound) placed between the transducer and the skin. This wave is partially reflected by the skin, while the other part penetrates and propagates through the skin with a direction parallel to the direction of oscillation. During its propagation, the wave is partially scattered and absorbed by the medium, resulting in attenuation of the emitted wave. An increase in temperature of the exposed medium is thus induced by the conversion of the ultrasound energy into heat.

The effects of ultrasound on the skin in terms of tolerance and efficacy of transdermal transport are directly related to the different ultrasound parameters i.e., frequency, intensity, and mode and time of application of the emitted wave.

43.2.1 Frequency

The frequency f of the emitted wave depends on the size and the geometry of the ultrasound transducer. The frequency range of ultrasound is generally defined as higher than 20 kHz. In-depth penetration of the acoustic wave into the skin is inversely proportional to the frequency; hence, the biological effects of high-frequency ultrasound are mainly located at the skin surface (i.e., stratum corneum and epidermis), while low-frequency ultrasound may interact with deeper located structures (i.e., dermis, hypodermis, and muscles). Frequencies ranging from 0.8 to 2 MHz were first used (3, 14), then higher frequencies ranging from 3 to 20 MHz were investigated, with the idea of concentrating the acoustic energy on the SC (15, 16). Finally, low-frequency ultrasound (20 to 150 kHz) has been shown to enhance transdermal transport more effectively (6–9, 17).

43.2.2 Mode

The ultrasound waves can be emitted continuously (continuous mode) or in a sequential mode, for example, 0.1 second applied every second (discontinuous or pulsed mode). Pulsed mode is used in preference to continuous mode in order to avoid faster and more intense rises in temperature in or at the skin surface.

43.2.3 Intensity

Intensity I is equal to $I = c \times E$, where E is the emitted acoustic energy (E) and c is the speed of the ultrasound wave in the medium. In human soft tissues the value of c is ~1500 m/sec. The energy E